UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/728,616	12/01/2000	Arlindo L. Castelhano	1919/60390-G/JPW/GJG/CMR	5191

7590 07/28/2004

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/728,616	CASTELHANO ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-110,114-124,128-131 and 133-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *76-98* is/are allowed.

6)☒ Claim(s) *99,103-109,117,118 and 133-135* is/are rejected.

7)☒ Claim(s) *100-102,110, 114-116,119-124 and 128-131* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed May 18, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 76, 123, 124, and 133 have been amended.

Claims 126 and 127 have been canceled.

Remarks drawn to rejections of Office Action mailed February 11, 2004 include:

Claim objections: which have been overcome by applicant's amendments and have been withdrawn.

Double Patenting Rejections: which have been overcome in part and withdrawn in part.

112 2nd paragraph rejections: which have been overcome by applicant's amendments and have been withdrawn.

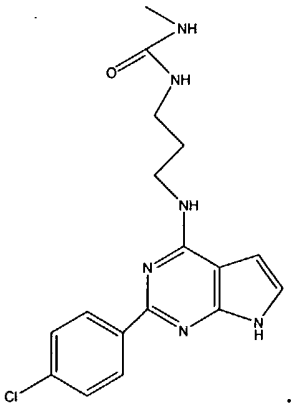
102(a) rejection: which has been overcome by applicant's amendments and has been withdrawn.

An action on the merits of claims 76-110, 114-124, 128-131, and 133-135 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Double Patenting

The rejection of claim 76 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 10 of U.S. Patent No. 6,686,366 is withdrawn as applicants have amended the claims of the instant application to carve out the overlapping structures.

The rejection of claim 99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 4-6 U.S. Patent No. 6,686,366 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the Markush groups of both claim sets comprise a compound of the same structure. Claim 99 comprises a compound having the following structure:



Claims 1 and 4-6 of the '366 patent claim the identical compound wherein the variables of '366 are defined as: m=1 (in claim 6); R_1 (of claim 6) is aminomethyl; R_3 is substituted aryl (chlorine substituted on benzene); and R_5 and R_6 are H.

Applicant's arguments filed May 18, 2004 have been fully considered but they are not persuasive. Applicants argue that the compounds of the instant application are improvements of the previously filed application, and thus are patentable over the prior art Markush group. The examiner notes that the '366 patent is drawn to the identical compound as set forth in claim 99 of the instant application. Moreover, arguments that the instantly claimed compounds are "later filed improvements" are not sufficient to overcome the instant rejection. Absent of a proof to the contrary, clearly setting forth the "improvements" of the compound as set forth in the instant application, the rejection is maintained as proper.

The rejection of claims 124, and 126-131 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-29 of U.S. Patent No. 6,686,366 is withdrawn due to applicant's canceling claims 126-127 and amending claim 76 (from which 124 depends) to carve out the compounds of the prior art.

The rejection of claims 133-135 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46 of U.S. Patent No. 6,686,366 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to methods of preparing the same class of compounds with identical methodological steps and identical reactants. It is noted that the chemical process that is occurring is an expected reaction based upon the prior art. The use of a novel and unobvious starting material, or a novel and unobvious final product, does

not render an obvious, predictable process patentable. In a chemical process, all of the evidence must be considered on the subject matter as a whole from the viewpoint of one skilled in the art, in the determination of obviousness, and not simply to the patentability of one of the starting materials or final products in the process. The process is deemed obvious to one of ordinary skill in t the art in view of the '366 patent since it involves a predictable and expected reaction, namely, the same reaction steps as the prior arts patent. See ***In re Durden, 763 F.2d 1405, 226 USPQ 359 (Fed Cir 1985).***

The rejection of claim 76 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7 and 8 of U.S. Patent No. 6,680,322 is withdrawn as applicants have amended claim 76 to carve out the compounds of the '322 patent.

The rejection of claims 124, 127, and 129-131 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-33 of U.S. Patent No. 6,680,322 is withdrawn due to applicant's canceling claims 126-127 and amending claim 76 (from which 124 depends) to carve out the compounds of the prior art.

The rejection of claim 133 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 36 of U.S. Patent No. 6,680,322 is maintained for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to methods of preparing the same class of compounds with identical methodological steps and identical reactants. It is noted that

the chemical process that is occurring is an expected reaction based upon the prior art. The use of a novel and unobvious starting material, or a novel and unobvious final product, does not render an obvious, predictable process patentable. In a chemical process, all of the evidence must be considered on the subject matter as a whole from the viewpoint of one skilled in the art, in the determination of obviousness, and not simply to the patentability of one of the starting materials or final products in the process. The process is deemed obvious to one of ordinary skill in t the art in view of the '366 patent since it involves a predictable and expected reaction, namely, the same reaction steps as the prior arts patent. See ***In re Durden, 763 F.2d 1405, 226 USPQ 359 (Fed Cir 1985).***

It is noted that a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 103-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)***. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims are drawn to prodrugs of the compounds of claim 76 or 99 wherein the prodrug is metabolized *in vivo* by a human subject to an active drug which selectively inhibits the A3 adenosine receptor wherein the prodrug is various esters, acetal groups, ketal groups, N-Mannich bases, imines, Schiff bases, oximes, acetals, enol esters, oxazolidines, or thiazolidines.

The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. The breadth of the claims includes all of the hundreds of thousands of prodrugs of the formula of claim 76 and 99 as well as the presently unknown list potential prodrug derivatives embraced by claim 103.

The state of the prior art

Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596, in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

The level of one of ordinary skill

Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience.

The level of predictability in the art

Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written.

The existence of working examples

There is no working example of any prodrug of a compound of claim 76 or 99.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any composition produced by the method of claim 4 to prevent the development of cancer without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation.

Thus, undue experimentation will be required to determine if any particular compound is, in fact, a prodrug.

Claims 117 and 118 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the actual condition which is being treated. The claim is drawn to treating "diseases associated with an A3 adenosine receptor" which is "associated with mast cell degradation". The examiner is unclear as to exactly what is intended to be treated in the instantly set forth claim.

All claims which depend from an indefinite claim are also indefinite. ***Ex parte Cordova, 10 U.S.P.Q. 2d 1949, 1952 (P.T.O. Bd. App. 1989).***

Conclusion

Claims 76-98 are allowed.

Claims 100-102, 110, 114-116, 119-124 and 128-131 are objected to as being dependent upon a rejected base claim.

A shortened statutory period for reply to this action is set to expire THREE MONTHS from the mailing date of this action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
July 15, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

BRUCK KIFLE, PH.D.
PRIMARY EXAMINER